### D. Efficacy Analysis

Clinical trial DE031 was designed to study the safety and efficacy of adding adalimumab to DMARD regimens encountered in a typical clinical practice. Adalimumab was given alone or in combination with other DMARDs that patients were already receiving. The study assessed the efficacy of adalimumab (40 mg) administered subcutaneously every other week for up to 24 weeks in patients with RA whose disease was not adequately treated with their current antirheumatic therapies. The efficacy assessment was a comparison of the ACR20 response rates (using CRP as the acute phase reactant) between adalimumab and placebo treatments. Adalimumab demonstrated a greater degree of improvement (53%) than placebo (35%) for the observed ACR20 response rate at Week 24 (Table 51).

**Table 51 : Study DE031 :ACR20 response rate: number (%) of patients responding over time by randomized treatment group (full analysis set)**

| | Adalimumab (N=315) | Placebo (N=315) |
|---|---|---|
| Time point | N (%) | N (%) |
| Week 2 | 104 (33.0) [a] | 27 (8.6) |
| Week 4 | 124 (39.4) [a] | 55 (17.5) |
| Week 8 | 159 (50.5) [a] | 76 (24.1) |
| Week 12 | 163 (51.7) [a] | 93 (29.5) |
| Week 16 | 165 (52.4) [a] | 100 (31.7) |
| Week 20 | 177 (56.2) [a] | 107 (34.0) |
| Week 24 | 167 (53.0) [a] | 110 (34.9) |
| LOCF Week 24 | 172 (54.6) | 112 (35.6) |

[a] Statistically significantly different from placebo ($p<0.001$).

Patients with an initiation of a new DMARD were counted as non-responders after initiation of DMARD.

Since this study was designed to approximate usual clinical practice, use of intra-articular injections and the ability to adjustment of DMARD and corticosteroid doses were permitted. The frequency of increases in DMARD and corticosteroid dosing was higher in the placebo group (Table 53) which would tend to increase the placebo response rate disproportionately. This may have contributed to the relatively high 35% ACR20 response rate at Week 24 (the highest ACR20 placebo response observed in the clinical development program, when compared to the placebo responses in trials DE009 [13%], DE011 [19%], and DE019 [30%]).

ACR20 response rates are displayed graphically over the 24 week time course for adalimumab-treated patients and placebo-treated patients in Figure 13. The onset of this response was rapid and sustained.

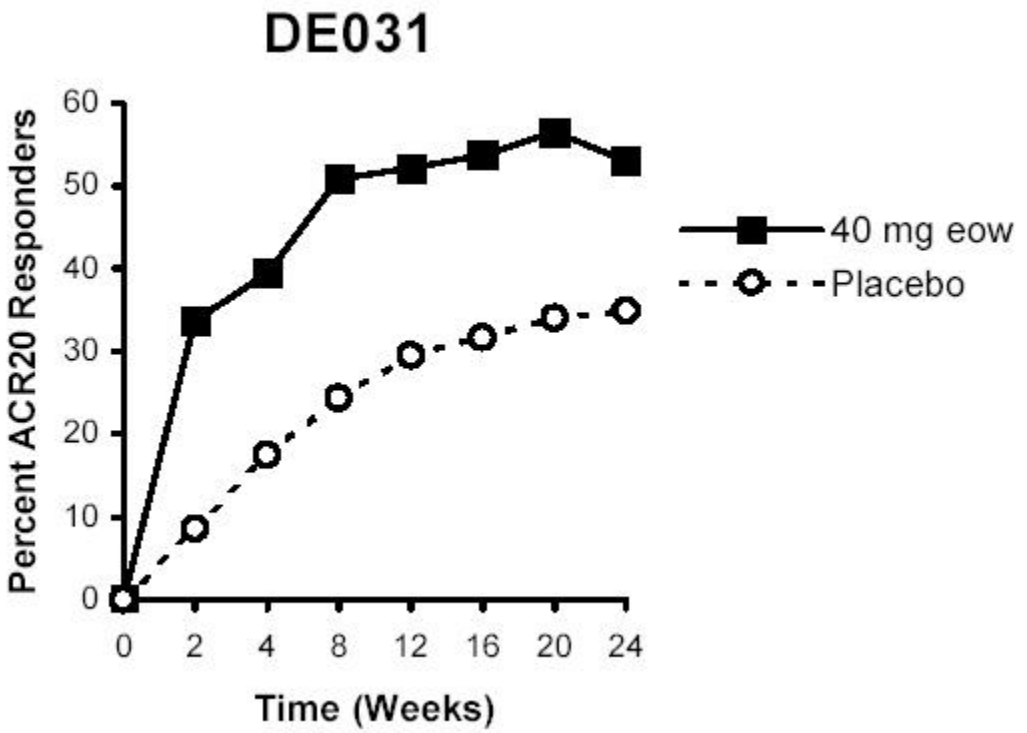



**Figure 13 : Study DE031 :Time course of ACR20 responses by randomized treatment group**

Adalimumab-treated patients taking concomitant methotrexate, antimalarial treatments, or sulfasalazine demonstrated a higher ACR20 response rate than placebo patients taking similar DMARDs. However, adalimumab patients taking concomitant leflunomide had a similar ACR20 response rate to placebo at Week 24 (33% and 37%, respectively) (Table 52). The patients receiving concomitant leflunomide were examined in more detail to determine whether there was a reduced treatment effect of adalimumab when added to leflunomide. First, earlier responses than Week 24 were examined. At Week 12, the ACR20 response rate for the adalimumab patients taking concomitant leflunomide was 41%, and for placebo plus leflunomide was 17%.

The lower response rate at Week 24 for adalimumab patients treated with leflunomide may have been influenced by a number of factors:

1). The higher number of patient withdrawals in the adalimumab plus concomitant leflunomide group. Of the patients receiving concomitant leflunomide, 7 of 42 (17%) adalimumab-treated patients but only 3 of 46 (7%) placebo-treated patients were withdrawn from the study prematurely. There was no pattern of reasons for withdrawal in either group. Of note, three of the adalimumab-treated early withdrawal patients had demonstrated ACR20 responses prior to being withdrawn, compared to one of the placebo-treated early withdrawal patients.

2). Patients treated with placebo plus concomitant leflunomide had an increase in ACR20 response from Week 12 to 24 probably due to the greater use of rescue steroids in this group (30%) compared to adalimumab plus concomitant leflunomide (14%). Among patients taking concomitant leflunomide, 5 of 46 (11%) placebo patients but only 1 of 42 (2%) adalimumab-treated patients received rescue steroid treatment before reaching ACR20 criteria.

Furthermore, thirty-five of the placebo plus leflunomide patients in this study rolled over into DE020, an open-label adalimumab 40 mg biweekly study. Their ACR20 response rate increased from 23% at study entry to 54% at Week 12.

Thus, the early withdrawals may have decreased the overall adalimumab-treated patient response, and the higher ACR20 response rate demonstrated by the placebo-treated patients in this study could be attributed to the greater rescue initiation of DMARDs, increased dosages of DMARDs and steroids, and intra-articular injections (Table 53). Data detailing the frequency and medications utilized for intra-articular injections were not provided.

**Table 52: Study DE031 : Concomitant Medication at Week 24 for ACR20**

| | **ACR 20** | | | |
|---|---|---|---|---|
| | **Adalimumab** | | **Placebo** | |
| Concomitant medication | **Total N** | **% Response** | **Total N** | **% Response** |
| Methotrexate | 178 | 57 | 199 | 35 |
| Antimalarial | 75 | 51 | 82 | 33 |
| Leflunomide | 42 | 33 | 46 | 37 |
| Sulfasalazine | 29 | 59 | 33 | 24 |
| Other DMARDs | 25 | 52 | 25 | 44 |
| No DMARD | 54 | 50 | 45 | 33 |
| One DMARD | 184 | 55 | 172 | 38 |
| Two DMARDs | 66 | 50 | 84 | 30 |
| Three or more DMARDs | 11 | 46 | 14 | 36 |

Antimalarial (e.g., HCG, chloroquine)

**Table 53: Study DE031 : Incidence of DMARD or Steroid Therapy Change**

| | Adalimumab (N=315) | Placebo (N=315) |
|---|---|---|
| Therapy change | N (%) | N (%) |
| Increase in dose of DMARD therapy | 6 (1.9) | 14 (4.4) |
| Increase in dose of steroid therapy | 14 (4.4) | 20 (6.3) |
| Initiation of DMARD | 3 (1.0) | 8 (2.5) |
| Total | 23 (7.3) | 42 (13.3) |

### E. Summary of Analyses for Study DE031

This trial was designed to mimic typical clinical practice where adalimumab would be given alone or in combination with other DMARDs. The study assessed the efficacy of adalimumab administered 40 mg subcutaneously every other week for up to 24 weeks to patients with RA whose disease was not adequately treated with their current antirheumatic therapies. The efficacy assessment, a comparison of the ACR20 responses, demonstrated a greater degree of improvement in the adalimumab-treated patients (53%) than placebo (35%) at 24 weeks. Similar efficacy was seen for adalimumab regardless of the background DMARD regimen

Comparable percentages of patients in the adalimumab and placebo treatment groups reported one or more treatment-emergent AEs during the study. However AEs considered to be at least possibly related to study drug were more frequent in the adalimumab group than in the placebo group. Injection site reaction was seen more frequently in patients receiving adalimumab than in patients receiving placebo. The incidence of infections was similar for patients in the adalimumab and placebo treatment groups. The proportion of adalimumab-treated patients experiencing serious infections was similar to placebo-treated controls. However, there was one death in the adalimumab-treatment group in a patient with herpes zoster complicated by streptococcal superinfection (necrotizing fasciitis). No pattern of an increase in AEs or SAEs was seen when adalimumab was combined with any specific DMARD or combination of DMARDs.

A higher proportion of patients in the adalimumab-treated group experienced malignancies compared to the placebo–treated patients. The malignancies observed in the adalimumab-treated patients were three cases of basal cell carcinoma and one case of T-cell lymphoma. The rate of malignancies in patients receiving adalimumab will be considered further in the Integrated Safety Analysis

A higher percentage of adalimumab-treated patients converted from negative to positive ANA and positive anti-dsDNA than placebo-treated patients during this trial. No clinical autoimmune disease was observed. The evidence of auto antibodies and autoimmune disease will be discussed further in the Integrated Safety Analysis.

## VI. Integrated Safety Analysis

### A. Safety Database

Safety data from all US and non-US (Europe, Australia, and Canada) sources that were available as of August 31, 2001 were integrated within this integrated summary of safety information (hereafter referred to as the 'ISS') to provide a comprehensive safety profile for adalimumab in this patient population. Safety data related to deaths, malignancies, serious adverse events, and serious infections were up-dated as of August 31, 2002. A total of 20 clinical trials completed during the adalimumab clinical development program are included in the integrated safety database (Table 54).

**Table 54: ISS : Studies contributing safety information to the adalimumab integrated safety database**

| Study category | Study | Location | Study characteristics | Dose(s) of adalimumab and route | Duration of study | Number enrolled |
|---|---|---|---|---|---|---|
| Clinical pharmacology studies in healthy volunteers | DE015 | NA | Bioequivalence study in healthy volunteers | 40 mg subcutaneous or intravenous | Single dose | 61 |
| | DE024C | EU | Pharmacokinetic/bioequivalence study in healthy volunteers | 0.1, 0.3, 1.0 mg/kg subcutaneous; 1.0 mg/kg intravenous | Single dose | 80 |
| | DE029 | NA | Bioequivalence study in healthy volunteers | 40 mg subcutaneous | Single dose | 120 |
| Clinical pharmacology studies in RA patients | DE001/DE003 (pbo-ctrl) | EU | Multi-center, placebo-controlled | 0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg, intravenous | ≥6 weeks | 120 |
| | DE004 (pbo-ctrl) | EU | Multicenter, placebo-controlled | 0.5 mg/kg weekly, subcutaneous | 12 weeks | 24 |
| | DE005/DE005X (pbo-ctrl) | NA | Multicenter, placebo-controlled, with concomitant MTX | 0.25, 0.5, 1.0, 3.0, or 5.0 mg/kg, intravenous | ≥6 weeks | 60 |
| | DE007 (pbo-ctrl) | EU | Multicenter, placebo-controlled | 20, 40 or 80 mg weekly, subcutaneous | 12 weeks | 284 |
| | DE010 (pbo-ctrl) | EU | Multicenter, placebo-controlled, with concomitant MTX | 1.0 mg/kg, intravenous or subcutaneous | ≥6 weeks | 54 |
| Adequate and well-controlled studies | DE009 | NA | Multicenter, placebo-controlled, in patients concomitantly treated with MTX | 20, 40, or 80 mg every other week, subcutaneous | 24 weeks | 271 |
| | DE011 | EU, AUS, CAN | Multicenter, placebo-controlled, with no concomitant DMARDs | 20 or 40 mg, weekly or every other week, subcutaneous | 26 weeks | 544 |
| | DE019 | NA | Multicenter, placebo-controlled, with MTX, investigates joint erosion | 20 mg weekly or 40 mg every other week, subcutaneous | 52 weeks | 619 |
| | DE031 | NA | Multicenter, placebo-controlled, with DMARDs, NSAIDs, or steroids | 40 mg every other week, subcutaneous | 24 weeks | 636 |
| Open-label continuation studies or phases | DE003 | EU | Continuation of DE001/DE003 (pbo-ctrl) | 0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg every other week, intravenous | 24 months | 117 |
| | DE004 | EU | Continuation of DE004 (pbo-ctrl) | 0.5 or 1.0 mg/kg weekly, subcutaneous | 2.5 years | 22 |
| | DE005X | NA | Continuation of DE005 in RA patients concomitantly treated with MTX | All patients transition to 40 mg every other week, subcutaneous | 26 months | 58 |
| | DE007 (2 yr)[a] | EU | Open-label continuation of DE007 (1 yr), with 3 dose levels in RA patients | 20, 40 or 80 mg weekly, subcutaneous | 2 years | 271 |
| | DE009X | NA | Continuation of DE009, in patients concomitantly treated with MTX | 40 mg every other week, subcutaneous | 6 months | 250 |
| | DE010 | EU | Continuation of DE010 (pbo-ctrl), in RA patients with concomitant MTX | 1.0 mg/kg every other week, subcutaneous | 2.5 years | 53 |
| | DE018 | EU, AUS, CAN | Continuation for European studies DE003, DE004, DE007, DE010, DE011 | 40 mg every other or 40 mg weekly, subcutaneous | 96 weeks | 794 |
| | DE020 | NA | Continuation for North American studies DE005X, DE009X, and DE031 | 40 mg every other week, subcutaneous | Open-ended | 810 |

Source of data: sponsor's ISS Table 1
AUS: Australia ; EU: Europe ; NA : North America (including U.S. and Canada) ; CAN : Canada
MTX = methotrexate ; pbo-ctrl = placebo-controlled
[a] Includes a 9-month blinded continuation period that followed DE017

The overall body of adalimumab safety data presented in this section evaluates safety concerns related to:

- The short- and long-term safety and tolerability of adalimumab.
- Safety of adalimumab when used alone or in combination with methotrexate or other DMARDs.
- Safety of adalimumab when administered subcutaneously at the recommended dose of 40 mg every other week, and at the higher dose of 40 mg weekly.
- Adverse events (AEs) experienced by RA patients treated with adalimumab, frequency and severity.

- Incidences and types of serious infections, malignancies, autoimmune disorders, and deaths associated with adalimumab treatment, particularly in patients exposed to higher than recommended doses.
- Incidence and effects of elevated anti-nuclear antibodies (ANAs), anti-double stranded deoxyribonucleic acid (anti-dsDNA) titers, and human anti-human antibodies (HAHAs) observed in some RA patients treated with adalimumab.
- Any apparent effect on the safety profile of adalimumab by the development of HAHAs or by prolonged dose interruptions.

Overall, the mean age of the patients treated with adalimumab was 55 years. Most adalimumab-treated patients (77%) were female, and the majority of adalimumab-treated patients (91%) were Caucasian. The mean duration of RA was 131 months and 80% of subjects were RF positive at baseline. Many of the patients were receiving DMARDs at baseline and during the studies. Concomitant medications included MTX in 49% of all patients and corticosteroids in 57%. With regard to co-morbid conditions among patients, hypertension was reported in 27%, diabetes in 6%, COPD in 4%, and CHF in 1% of patients**.**

A total of approximately 1600 patients received treatment with adalimumab at the proposed dosage of 40 mg biweekly for ≥ 6 months and approximately 800 patients received treatment at that dose for ≥ 12 months (Table 55). The supplemental safety update provided safety data for approximately 2400 adalimumab-treated patients.

**Table 55: ISS : Summary of the Duration of Exposure to Adalimumab by Treatment Received in all RA Patients**

| | Adalimumab | | | | | | |
|---|---|---|---|---|---|---|---|
| **Duration of exposure**[a] | 20 mg Q2w sc (N=175) N (%) | 20 mg wk sc (N=397) N (%) | **40 mg Q2w sc (N=1903) N (%)** | 40 mg wk sc (N=466) N (%) | All sc doses[b] (N=2263) N (%) | All iv doses[c] (N=197) N (%) | All adalimumab (N=2334) N (%) |
| **<3 month** | 23 (13) | 39 (10) | **117 (6)** | 55 (12) | 95 (4) | 31 (16) | 109 (5) |
| **3-<6 months** | 41 (23) | 49 (12) | **193 (10)** | 78 (17) | 139 (6) | 17 (9) | 152 (7) |
| **6-<12 months** | 111 (63) | 108 (27) | **798 (42)** | 151 (32) | 593 (26) | 14 (7) | 576 (25) |
| **12-<18 months** | 0 (0) | 200 (50) | **669 (35)** | 88 (19) | 945 (42) | 46 (23) | 908 (39) |
| **18-<24 months** | 0 (0) | 0 (0) | **122 (6)** | 48 (10) | 214 (10) | 9 (5) | 195 (8) |
| **24-<36 months** | 0 (0) | 1 (0) | **4 (0)** | 46 (10) | 195 (9) | 32 (16) | 241 (10) |
| **36-<48 months** | 0 (0) | 0 (0) | **0 (0)** | 0 (0) | 82 (4) | 48 (24) | 108 (5) |
| [3] **48 months** | 0 (0) | 0 (0) | **0 (0)** | 0 (0) | 0 (0) | 0 (0) | 45 (2) |

wk = weekly Q2w = every other week sc = subcutaneous iv = intravenous

[a] The duration intervals are defined as follows: <3 months = 1-90 days; 3-<6 months = 91-163 days; 6-<12 months = 164-344 days; 12-<18 months = 345-527 days; 18-<24 months = 528-709 days; 24-<36 months = 710-1074 days; 36-<48 months = 1075-1439 days; ≥48 months = ≥1440 days.

[b] includes 80 (1.0 mg/kg) eow or wk.

[c] 0.25, 0.50, 1.0, 3.0, 5.0, 10.0 mg/kg eow or wk.

### B. Treatment-Emergent Adverse Events

Table 56 presents an overview of adverse events observed during the adequate and well-controlled trials. Because patients receiving different regimens had widely varying duration of exposure, rates are calculated as events per 100 patient-years to provide a common metric. Four categories of events of special interest were observed to occur among patients at a higher frequency per 100 patient-years in the adalimumab-treatment groups compared to placebo: deaths, drug-related AEs, deaths, malignancies, and infections (serious and non-serious). These will be described in more detail.

**Table 56 : ISS : Overview of number (number/100 patient years) of patients with treatment-emergent AEs during the placebo-controlled period, by randomized treatment – adequate and well-controlled studies (safety set)**

| | Adalimumab | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 mg Q2w sc (N=175) | | 20 mg wk sc (N=324) | | **40 mg Q2w sc (N=705)** | | 40 mg wk sc (N=103) | | 80 mg Q2w sc (N=73) | | All adalimumab (N=1380) | | **Placebo (N=690)** | |
| **Patients with any [a]** | N (N/100PY) | | N (N/100PY) | | **N (N/100PY)** | | N (N/100PY) | | N (N/100PY) | | N (N/100PY) | | **N (N/100PY)** | |
| **AE** | 170 | (238) | 312 | (132) | **638** | **(160)** | 102 | (211) | 64 | (205) | 1286 | (164) | **598** | **(165)** |
| **Clinical AE** | 165 | (231) | 298 | (126) | **620** | **(156)** | 97 | (201) | 64 | (205) | 1244 | (158) | **573** | **(158)** |
| **Laboratory AE** | 106 | (148) | 152 | (64) | **216** | **(54)** | 89 | (184) | 6 | (19) | 569 | (72) | **178** | **(49)** |
| **Fatal AE** | 0 | (0.0) | 1 | (0.4) | **5** | **(1.3)** | 1 | (2.1) | 0 | (0) | **7** | **(0.9)** | **1** | **(0.3)** |
| **SAE** | 17 | (24) | 53 | (23) | **61** | **(15)** | 14 | (29) | 6 | (19) | 151 | (19) | **60** | **(17)** |
| **AE leading to withdrawal** | 11 | (15) | 27 | (11) | **45** | **(11)** | 5 | (10) | 3 | (10) | 91 | (12) | **29** | **(8)** |
| **AE leading to dose interruption** | 16 | (22) | 74 | (31) | **103** | **(26)** | 17 | (35) | 14 | (45) | 224 | (29) | **86** | **(24)** |
| **AE leading to dose reduction** | 0 | (0.0) | 1 | (0) | **0** | **(0)** | 0 | (0) | 0 | (0) | 1 | (0) | **0** | **(0)** |
| **Severe or life-threatening/intractable AE** | 45 | (63) | 83 | (35) | **113** | **(28)** | 22 | (46) | 7 | (22) | 270 | (34) | **114** | **(32)** |
| **At least possibly drug-related AE** | 112 | (156.7) | 198 | (84.0) | **376** | **(94)** | 71 | (146.9) | 35 | (112.0) | 792 | (100.8) | **280** | **(77)** |
| **Infection (serious and non-serious)** | 93 | (130.1) | 196 | (83.1) | **398** | **(100)** | 51 | (105.5) | 45 | (144.1) | 783 | (99.7) | **334** | **(92)** |
| **Serious infection** | 2 | (2.8) | 10 | (4.2) | **18** | **(4.5)** | 3 | (6.2) | 1 | (3.2) | 34 | (4.3) | **7** | **(1.9)** |
| **Malignancy** | 2 | (2.8) | 5 | (2.1) | **10** | **(2.5)** | 1 | (2.1) | 1 | (3.2) | 19 | (2.4) | **2** | **(<1)** |
| **Immunologic reaction** | 1 | (1.4) | 2 | (0.8) | **6** | **(1.5)** | 1 | (2.1) | 0 | (0) | 10 | (1.3) | **4** | **(1.1)** |

wk = weekly Q2w = every other week sc = subcutaneous

[a] More than one AE per patient possible.

The most frequently observed adverse drug reactions were injection site reactions, rhinitis, upper respiratory infection, abnormal laboratory test, and rash.

The rate of adverse events was approximately one AE per year and one serious event per 4 to 5 years among adalimumab-treated and placebo-treated patients. Adalimumab-treated patients experienced a higher incidence of laboratory AEs and serious infections (Table 57).

**Table 57 : ISS :Overview of number (%) of patients with treatment-emergent AEs in patients treated with adalimumab during placebo-controlled and non-placebo-controlled periods, by treatment received – all studies in RA patients (safety set)**

| | Adalimumab 40 mg Q2w sc (N=1903) | | | | All adalimumab doses sc and iv (N=2334) | | | | Placebo-Treated Patients from the Adequate and Well-Controlled Studies (N=690) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients with any[a]** | **N** | **(%)** | **E (E/100 pt-yrs)** | | **N** | **(%)** | **E (E/100 pt-yrs)** | | **N** | **(%)** | **E (E/100 pt-yrs)** | |
| AE | 1765 | (93) | 12172 | **(786)** | 2221 | (95) | 30775 | **(1042)** | 589 | (87) | 3304 | **(912)** |
| Clinical AE | **1675** | **(88)** | **9003** | **(582)** | **2180** | **(93)** | **19699** | **(667)** | **573** | **(83)** | **2769** | **(764)** |
| Laboratory AE | **886** | **(47)** | **3169** | **(205)** | **1201** | **(52)** | **11076** | **(375)** | **178** | **(26)** | **535** | **(148)** |
| Fatal AE[b] | 9 | (1) | 16 | **(1)** | 22 | (1) | 41 | **(1)** | 1 | (0) | 3 | **(1)** |
| SAE | 294 | (15) | 404 | **(26)** | 575 | (25) | 1022 | **(35)** | 60 | (9) | 75 | **(21)** |
| AE leading to withdrawal | 114 | (6) | 162 | **(11)** | 252 | (11) | 353 | **(12)** | 29 | (4) | 39 | **(11)** |
| AE leading to dose interruption | 340 | (18) | 522 | **(34)** | 614 | (26) | 1106 | **(37)** | 86 | (13) | 124 | **(34)** |
| AE leading to dose reduction | 2 | (0) | 2 | **(0)** | 23 | (1) | 43 | **(2)** | 0 | (0) | 0 | **(0)** |
| Severe or life-threatening/intractable AE | 372 | (20) | 610 | **(39)** | 734 | (31) | 1482 | **(50)** | 114 | (17) | 220 | **(61)** |
| At least possibly drug-related AE | 984 | (52) | 3214 | **(208)** | 1550 | (66) | 8620 | **(292)** | 280 | (41) | 850 | **(235)** |
| Infection (serious and non-serious) | 1061 | (56) | 2209 | **(143)** | 1573 | (67) | 4507 | **(153)** | 334 | (48) | 591 | **(163)** |
| Serious infection | 56 | (3) | 61 | **(4)** | 129 | (6) | 146 | **(5)** | 7 | (1) | 7 | **(2)** |
| Malignancy | 29 | (2) | 30 | **(2)** | 52 | (2) | 53 | **(2)** | 2 | (0) | 2 | **(1)** |
| Immunologic reaction | 16 | (1) | 19 | **(1)** | 38 | (2) | 49 | **(2)** | 4 | (1) | 4 | **(1)** |

Q2w = every other week sc = subcutaneous iv = intravenous

[a] More than one AE per patient possible.

[b] Can include more than one AE ongoing at time of death.

Increasing age among adalimumab-treated patients is associated with an increased frequency of occurrence of malignancies, SAEs, and AEs resulting in dose interruption (Table 58). These percentages increased as age increased over 65 and even higher over age 75 in both those patients treated with adalimumab and those receiving placebo. The percentage of patients with fatal AEs, which only occurred in the adalimumab–treated group, also increased in frequency with advancing age.

**Table 58 : ISS : Overview of number (%) of patients with treatment-emergent AEs, by age - adequate and well controlled studies (safety set)**

| | Adalimumab 40 mg Q2w sc | | | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 (N=526) | | ³65 (N=179) | | ³75 (N=42) | | <65 (N=520) | | ³65 (N=170) | | ³75 (N=34) | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Patients with any[a] AE | 475 | (90) | 163 | (91) | 39 | (93) | 457 | (88) | 141 | (83) | 25 | (74) |
| Clinical AE | 461 | (88) | 159 | (89) | 39 | (93) | 435 | (84) | 138 | (81) | 24 | (71) |
| Laboratory AE | 167 | (32) | 49 | (27) | 13 | (31) | 141 | (27) | 37 | (22) | 5 | (15) |
| **Fatal AE** | **0** | **( 0)** | **5** | **( 3)** | **3** | **( 7)** | **0** | **( 0)** | **1** | **( 1)** | **0** | **( 0)** |
| **SAE** | **31** | **( 6)** | **30** | **(17)** | **9** | **(21)** | **40** | **( 8)** | **20** | **(12)** | **5** | **(15)** |
| **AE leading to withdrawal** | **23** | **( 4)** | **22** | **(12)** | **5** | **(12)** | **18** | **( 4)** | **11** | **( 7)** | **4** | **(12)** |
| **AE leading to dose interruption** | **67** | **(13)** | **36** | **(20)** | **11** | **(26)** | **64** | **(12)** | **22** | **(13)** | **6** | **(18)** |
| AE leading to dose reduction | 0 | ( 0) | 0 | ( 0) | 0 | ( 0) | 0 | ( 0) | 0 | ( 0) | 0 | (.0) |
| Severe or life-threatening/intractable AE | 67 | (13) | 46 | (26) | 7 | (17) | 78 | (15) | 36 | (21) | 7 | (21) |
| At least possibly drug-related AE | 282 | (54) | 94 | (53) | 17 | (41) | 223 | (43) | 57 | (34) | 8 | (24) |
| Infection (serious and non-serious) | 303 | (58) | 95 | (53) | 21 | (50) | 258 | (50) | 76 | (45) | 14 | (41) |
| Serious infection | 7 | (1) | 11 | ( 6) | 2 | ( 5) | 4 | ( 1) | 3 | ( 2) | 1 | (3) |
| **Malignancy** | **7** | **( 1)** | **3** | **( 2)** | **2** | **( 5)** | **1** | **( 0)** | **1** | **( 1)** | **0** | **( 0)** |
| Immunologic reaction | 5 | ( 1) | 1 | (1) | 0 | ( 0) | 4 | ( 1) | 0 | ( 0) | 0 | ( 0) |

Q2w = every other week sc = subcutaneous

[a] More than one AE per patient possible.

### C. Other Adverse Events

Table 59 demonstrates the most frequently reported treatment-emergent AEs, irrespective of relation to study drug, in patients treated with adalimumab during placebo-controlled and non-placebo-controlled study periods, by treatment received.

**Table 59: ISS : Number (%) of patients with the most frequently reported treatment-emergent AEs, irrespective of relation to study drug, in patients treated with adalimumab during placebo-controlled and non-placebo-controlled study periods, by treatment received – all studies in RA patients**

| | Adalimumab 40 mg Q2w sc (N=1903) | | All adalimumab doses, sc and iv (N=2334) | | Placebo-Treated Patients from the Adequate and Well-Controlled Studies (N=690) | |
|---|---|---|---|---|---|---|
| **Body system/AE[b]** | **N (%)** | **E (E/100 pt-yrs)** | **N (%)** | **E (E/100 pt-yrs)** | **N (%)** | **E (E/100 pt-yrs)** |
| **Abdominal pain** | 111 (6) | 130 (8) | 222 (10) | 276 (9) | 30 (4) | 32 (9) |
| **Accidental Injury** | 183 (10) | 221 (14) | 309 (13) | 396 (13) | 56 (8) | 59 (16) |
| **Asthenia** | 104 (6) | 114 (7) | 224 (10) | 269 (9) | 40 (6) | 41 (11) |
| **Back pain** | 128 (7) | 140 (9) | 244 (11) | 325 (11) | 25 (4) | 29 (8) |
| **Clinical flare reaction** | 248 (13) | 306 (20) | 406 (17) | 600 (20) | 75 (11) | 89 (25) |
| **Fever** | 42 (2) | 48 (3) | 164 (7) | 239 (8) | 17 (3) | 18 (5) |
| **Flu syndrome** | 132 (7) | 148 (10) | 279 (12) | 392 (13) | 41 (6) | 43 (12) |
| **Infection** | 62 (3) | 63 (4) | 131 (6) | 145 (5) | 13 (2) | 14 (4) |
| **Surgery** | 108 (6) | 122 (8) | 208 (9) | 270 (9) | 23 (3) | 25 (7) |
| **Hypertension** | 99 (5) | 106 (7) | 218 (9) | 287 (10) | 18 (3) | 18 (5) |
| **Diarrhea** | 132 (7) | 163 (11) | 257 (11) | 350 (12) | 66 (10) | 86 (24) |
| **Nausea** | 134 (7) | 158 (10) | 265 (11) | 350 (12) | 54 (8) | 63 (17) |
| **Sore throat** | 98 (5) | 124 (8) | 190 (8) | 244 (8) | 39 (6) | 45 (14) |
| **Decreased hemoglobin** | **191 (10)** | **238 (15)** | **524 (23)** | **1077 (37)** | **44 (6)** | **49 (14)** |
| **Injection site pain** | **122 (6)** | **388 (25)** | **250 (11)** | **726 (25)** | **85 (12)** | **330 (91)** |
| **Injection site reaction** | **104 (6)** | **210 (14)** | **195 (8)** | **373 (13)** | **8 (1)** | **9 (3)** |
| **BUN increased** | 150 (8) | 194 (13) | 274 (12) | 532 (18) | 23 (3) | 32 (9) |
| **Peripheral edema** | 83 (4) | 97 (6) | 144 (6) | 176 (6) | 24 (4) | 27 (8) |
| **Arthralgia** | 84 (4) | 92 (6) | 185 (8) | 228 (8) | 43 (6) | 48 (13) |
| **Joint disorder** | 100 (5) | 114 (7) | 201 (9) | 250 (9) | 40 (6) | 43 (12) |
| **Dizziness** | 75 (4) | 91 (6) | 159 (7) | 228 (8) | 32 (5) | 36 (10) |
| **Headache** | 175 (9) | 245 (16) | 387 (17) | 646 (22) | 53 (8) | 67 (19) |
| **Depression** | 70 (4) | 74 (5) | 116 (5) | 129 (4) | 22 (3) | 27 (8) |
| **Bronchitis** | 116 (6.1) | 133 (9) | 242 (10) | 324 (11) | 35 (5) | 42 (12) |
| **Cough increased** | 109 (5.7) | 127 (8) | 242 (10) | 294 (10) | 42 (6) | 45 (12) |
| **Rhinitis** | 280 (15) | 376 (24) | 533 (23) | 858 (29) | 93 (14) | 106 (29) |
| **Sinusitis** | 178 (9) | 234 (15) | 275 (12) | 389 (13) | 61 (9) | 78 (22) |
| **Upper respiratory infection** | 294 (15) | 373 (24) | 430 (18) | 585 (20) | 86 (13) | 96 (27) |
| **Herpes simplex** | 65 (3) | 77 (5) | 131 (6) | 183 (6) | 15 (2) | 21 (6) |
| **Pruritus** | 72 (4) | 80 (5) | 237 (10) | 310 (11) | 10 (1) | 11 (3) |
| **Rash** | 205 (11) | 237 (15) | 432 (19) | 600 (20) | 43 (6) | 49 (14) |
| **Skin disorder** | 77 (4) | 86 (6) | 172 (7) | 215 (7) | 20 (3) | 23 (6) |
| **Hematuria** | 47 (3) | 58 (4) | 241 (10) | 424 (14) | 28 (4) | 41 (11) |
| **Urinary tract infection** | 129 (7) | 160 (10) | 195 (8) | 251 (9) | 36 (5) | 50 (14) |

Q2w = every other week sc = subcutaneous iv = intravenous

[a] Occurring in ≥5% of patients in the "all adalimumab" treatment group.

## D. Deaths and Comparable Mortality Rates

Eight patients, 7 treated with adalimumab and 1 treated with placebo died, as a result of AEs during the adequate and well-controlled studies; the primary AE leading to death is presented by patient in Table 60. Deaths occurred at a rate of 0.3/100 patient-years (CI, 0.26, 0.82) among placebo-treated patients, 0.9/100 patient-years (CI, 0.23, 1.55) among all adalimumab-treated patients, and 1.3/100 patient-years (CI, 0.16, 2.35) among patients receiving the proposed recommended dose. Two additional deaths among adalimumab-treated patients (total of 9) are provided in supplementary final safety updates: 1.) diverticulitis with secondary sepsis and 2.) hepatic necrosis. The most frequent causes of death were sepsis (3) and malignancy (3) [carcinoma (2) and lymphoma (1)]. Two deaths related to infection are described in greater detail in Table 61.

**Table 60 : ISS : Patients with fatal AEs – Adequate and Well-Controlled Studies**

| Study | Pt. No. | Age, sex | Treatment | Adverse event[a] (HARTS term) | Adverse event (Investigator's term) | Day on drug at onset | Duration (days) |
|---|---|---|---|---|---|---|---|
| DE011 | 2120 | 78, M | Adalimumab 40 mg wk | Gastrointestinal carcinoma | Metastatic adenocarcinoma | 65 | 96 |
| | 4209 | 77, M | Adalimumab 40 mg eow | Carcinoma | Cholangiocarcinoma | 13 | 116 |
| | 4217 | 73, F | Placebo | Intestinal obstruction | Intestinal obstruction | 101 | 8 |
| | 4711 | 76, F | Adalimumab 40 mg eow | Myocardial infarction | Myocardial infarction[b] | 157 | 3 |
| DE019 | 1705 | 62, F | Adalimumab 20 mg wk | Lymphoma like reaction | B-cell lymphoma | 147 | 96 |
| | 1706 | 73, F | Adalimumab 40 mg eow | Bone fracture (not spontaneous) | Multiple fractures | 304 | 33 |
| | 8702 | 75, F | Adalimumab 40 mg eow | Sepsis | Septic shock | 115 | 14 |
| DE031 | 15106 | 70, M | Adalimumab 40 mg eow | Herpes zoster | Disseminated herpes | 11 | 16 |

F = female M = male wk = weekly eow = every other week

[a] Primary AE leading to death; more than one AE with fatal outcome per patient possible.

[b] Patient had a gastrointestinal bleed (Hgb drop 11.8 – 6.0 mg/dL) followed by a myocardial infarction.

**Table 61 : Deaths Related to Infections**

| Patient Number | Adverse Event | Relevant Medical History |
|---|---|---|
| 8702 | Urosepsis & septic shock | Onset fatigue and disturbance of equilibrium (incoordination), patient was withdrawn from study, and event resolved. Patient became febrile with urinary incontinence and a week later developed a urinary tract infection and a upper respiratory infection. Urosepsis (E. coli) was followed by septic shock and pancytopenia, cardiac arrest and death. |
| 15106 | Herpes zoster, dissemination, superinfection | Herpes zoster with dissemination, necrotizing fasciitis of upper extremity, superinfection with Group A streptococcus and death. |

Table 62 lists all 22 fatal adverse events from among all patients treated with adalimumab in the clinical development program. Two additional deaths (total of 24), one each from diverticulitis with associated sepsis and hepatic necrosis are not shown on this table. Even though the majority (77%) of patients enrolled in these studies were females, the majority of deaths occurred in male subjects (58% [14/24]). The major categories for the deaths include cardiovascular (7), malignancy (6), infections (5), and gastrointestinal (3), [including the additional death from diverticulitis and associated sepsis not shown on this Table].

**Table 62 : ISS : List of fatal adverse events during treatment with adalimumab. All patients treated with adalimumab. Study group: all studies in patients with RA (DE001/3, 004, 005/X, 010, 007, 009/X, 011, 019, 031, 018, 020).**

| | Category of Primary Cause of Death | Initial Study | Pt. No. | Age/ Sex | Adalimumab Treatment | Day on Drug at Onset | Fatal Adverse Event | Comments |
|---|---|---|---|---|---|---|---|---|
| 1 | Malignancy | DE010 | 209 | 56/M | 1 mg/kg sc q2w | 420 | Small cell carcinoma lung | |
| 2 | Malignancy | DE003 | 22 | 67/M | 3 mg/kg IV q4w | 599 | Prostate carcinoma | Metastatic |
| 3 | Malignancy | DE003 | 69 | 56/M | 0.5 mg/kg IV q4w | 812 | Non-Hodgkin lymphoma | Pancytopenia & sepsis |
| 4 | Malignancy | DE011 | 2120 | 78/M | 40 mg sc qw | 65 | Adenocarcinoma bowel | |
| 5 | Malignancy | DE011 | 4209 | 77/M | 40 mg sc q2w | 13 | Cholangiocarcinoma | |
| 6 | Malignancy | DE019 | 1705 | 62/F | 20 mg sc qw | 147 | B-cell lymphoma | |
| 7 | Gastrointestinal | DE001 | 23 | 54/M | 0.5 mg/kg IV q4w | 24 | Necrotizing pancreatitis | Suspected abscess of spleen |
| 8 | Infection | DE019 | 8702 | 75/F | 40 mg sc q2w | 115 | *E. coli* urosepsis | |
| 9 | Infection | DE007 | 2702 | 69/M | 40 mg sc qw | 420 | Aspergilloma | Abcesses and granulomata |
| 10 | Infection | DE018 | 1808 | 58/F | 40 mg sc q2w | 240 | Recurring foot infection | Septic myocarditis |
| 11 | Infection | DE018 | 801 | 43/F | 80 mg sc qw | 919 | Possible septic shock | Pulmonary macro-infiltrates |
| 12 | Infection | DE031 | 15106 | 70/M | 40 mg sc q2w | 11 | Necrotizing fasciitis | Herpes zoster arm; GA strep |
| 13 | Cardiovascular | DE009x | 1906 | 61M | 40 mg sc q2w | 166 | Abdominal aotic aneurysm | Surgery |
| 14 | Cardiovascular | DE010 | 215 | 38/F | 1 mg/kg sc q4w | 678 | Myocardial infarction | |
| 15 | Cardiovascular | DE011 | 4711 | 76/F | 40 mg sc q2w | 157 | Myocardial infarction | Gastrointestinal hemorrhage |
| 16 | Cardiovascular | DE003 | 105 | 55/M | 10 mg/kg IV q2w | 58 | Heart failure | Sudden death |
| 17 | Cardiovascular | DE004 | 13 | 78/F | 0.5 mg/kg sq q3w | 726 | Myocardial infarction | Sudden death |
| 18 | Cardiovascular | DE007 | 2015 | 65/M | 40 mg sc qw | 85 | Myocardial infarction | |
| 19 | Cardiovascular | DE020 | 707 | 69/M | 40 mg sc q2w | 417 | Heart failure | Dilated cardiomyopathy |
| 20 | Gastrointestinal | DE018 | 1417 | 72/F | 40 mg sc q2w | 322 | Diverticular sigmoiditis | Complications of repair |
| 21 | Trauma | DE019 | 1706 | 73/F | 40 mg sc q2w | 304 | Multiple fractures sec to fall | Complications of fall |
| 22 | Respiratory | DE003 | 19 | 71/M | 3 mg/kg IV q4w | 318 | Respiratory insufficiency | Interstitial fibrosis |

Because the adalimumab safety database includes a significant number of older patients, including a substantial portion aged 65 to 75 (22%) and over age 75 (5%), some deaths are expected. In addition, mortality has been reported to be increased in RA patients. To determine whether the death rate was higher than expected, the observed rate was compared to that expected among various populations (Table 63). Standardized Mortality Rate (SMR - ratio of observed death rate compared to age adjusted expected frequency) was 0.72 for all adalimumab-treated subjects (C.I., 0.46, 1.05), 1.38 for males (C.I., 0.72, 2.44) and 0.45 for females (C.I., 0.22, 0.83). The confidence interval for the male deaths overlaps 'one,' implying that the mortality rate observed was within the expected range. The mortality rate for the females was lower than expected. The SMR for adalimumab-treated patients did not exceed that observed in a variety of epidemiologic studies of RA patients

**Table 63 : ISS : Comparable Mortality Rates Among RA Patients**

| Study | Population Base | SMR* (95% CI) |
|---|---|---|
| **Wolfe et al (1994) [1]** | **Tertiary referral center (North America** | **1.98 - 3.08** |
| | **Community-based (North America)** | **1.98** |
| **Symmons et al (1998) [2]** | **Hospital-based referral center (England)** | **2.7 (2.4, 3.1)** |
| **Gabriel et al (1999) [3]** | **RA patients (All Rochester)** | **1.38 (1.22, 1.55)** |
| **Krause et al (2000) [4]** | **Methotrexate responders** | **1.47** |
| | **Methotrexate non-responders** | **4.11** |
| **Adalimumab clinical development program** | **Calculation using WHO mortality rates (22 adalimumab-treated patients that died)** | **0.72 (0.46, 1.05)** |
| | **Males (13)** | **1.38 (0.72, 2.44)** |
| | **Females (9)** | **0.45 (0.22, 0.83)** |

* Standardized Mortality Rate

Highest mortality rates associated with increased age, male sex, RF positivity, and continued signs of active inflammation

[1] Wolfe, F, Sibley TJ, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum.* 1994; **37**: 481-494.
[2] Symmons DPM, Jones MA, Scott DL, Prior P. Long-term mortality outcome in patients with RA: rarly presenters continue to do well. *J Rheumatol*. 1998; **25**: 1072-7.
[3] Gabriel AE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in four decades. *J Rheumatol*. 1999; **25**: 2529-2533.
[4] Krause D, Schleusser B, Herborn G, Rau R. Response to methotrxate treatment is associated with reduced mortality in patients with severe RA. *Arthritis Rheum.* 2000; **43**: 14-21.

## E. Serious Adverse Events

Overall the rate of SAEs was not higher among adalimumab-treated patients compared to placebo controls at the proposed recommended dose (Table 56). However, a higher rate of SAEs was observed among patients receiving 40 mg weekly.

To explore why SAEs were more frequent among patients receiving 40 mg weekly, the individual studies were examined. All 103 patients receiving that dose were in study DE011, the European monotherapy study. In that study, the rate of SAEs was lower among patients receiving adalimumab 40 mg weekly (22.6/100 patient−years) or adalimumab 40 mg biweekly (26.0/100 patient−years) than those receiving placebo (39.7/100 patient−years) [Table 64]. Thus, the rate of SAEs does not appear to be increased in patients receiving adalimumab 40 mg weekly.

For both adalimumab- and placebo-treated patients, the percentage of patients reporting SAEs was higher among patients >65 years of age than among patients <65 years of age, and higher still among the small group of patients >75 years of age (Table 95). Within each age group the overall percentage of SAEs was slightly higher among adalimumab-treated patients than among controls. During the double-blind placebo-controlled periods of the adequate and well-controlled studies, 151 adalimumab-treated patients (11% of 1380; 19 patients/100 pt-yrs) and 60 placebo-treated patients (9% of 690 ; 17 patients/100 pt-yrs) experienced one or more SAEs. SAEs reported slightly more frequently by adalimumab-treated patients included surgery, clinical flare reaction, bone fracture, and pneumonia.

The most commonly reported SAE was surgery, a HARTS term that encompassed arthroplasty and arthrodesis procedures (18 events in 17 patients), tendon repair, hernia repair, aneurysm repair, uterine prolapse repair, removal of fibroids, cholecystectomy, pacer placement revision, prostatectomy, and removal of a basal cell carcinoma (one patient each). Each of the five most commonly reported SAEs occurred more often among all adalimumab- than among placebo-treated patients. Ten percent of adalimumab-treated patients and 8 % of placebo-treated patients experiencd one or more SAEs other than planned surgeries

For both adalimumab- and placebo-treated patients, the percentage of patients reporting SAEs was not higher among patients taking corticosteroids at baseline than among patients not taking corticosteroids at baseline, and was not higher among patients taking concomitant MTX than among patients who were not (Table 97).

**Table 64 : Study DE011 : Overview of number (%) of patients with treatment-emergent AEs (safety set)**

| | Adalimumab 40 mg Q2w 50.07 pt-yrs (N=113) | | Adalimumab 40 mg Q2w 48.61 pt-yrs (N=103) | | Placebo 40.34 pt-yrs (N=110) | |
|---|---|---|---|---|---|---|
| | N (%) | N/100 pt-yrs | N (%) | N/100 pt-yrs | N (%) | N/100 pt-yrs |
| **Patients with any AE** [a] | 112 (99.1) | 223.7 | 102 (99.0) | 209.9 | 105 (95.5) | 260.3 |
| **Serious AE (SAE)** | 13 (11.5) | **26.0** | 11 (10.7) | **22.6** | 16 (14.5) | **39.7** |
| **Severe or life-threatening/intractable AE** | 27 (23.9) | 53.9 | 21 (20.4) | 43.2 | 25 (22.7) | 62.0 |
| **At least possibly drug- related AE** | 74 (65.5) | 147.8 | 69 (67.0) | 142.0 | 49 (44.5) | 121.5 |
| **AE leading to death** | 2 (1.8) | 4.0 | 1 (1.0) | 2.1 | 1 (0.9) | 2.5 |
| **AE leading to permanent withdrawal** | 7 (6.2) | 14.0 | 5 (4.9) | 10.3 | 3 (2.7) | 7.4 |
| **AE leading to temporary withdrawal** | 15 (13.3) | 30.0 | 15 (14.6) | 30.9 | 4 (3.6) | 9.9 |
| **AE leading to dose reduction** | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 |
| **AE leading to dose increase** | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 | 0 (0.0) | 0.0 |
| **AE leading to switch to rescue period** | 4 (3.5) | 8.0 | 0 (0.0) | 0.0 | 11 (10.0) | 27.3 |
| **Infection** | 56 (49.6) | 111.8 | 50 (48.5) | 102.9 | 43 (39.1) | 106.6 |
| **Serious infection** | 1 (0.9) | 2.0 | 2 (1.9) | 4.1 | 0 (0.0) | 0.0 |
| **Malignancy** | 2 (1.8) | 4.0 | 1 (1.0) | 2.1 | 1 (0.9) | 2.5 |
| **Immunologic reaction** | 1 (0.9) | 2.0 | 1 (1.0) | 2.1 | 0 (0.0) | 0.0 |

[a] More than one AE per patient possible.

## F. Malignancies and Comparative Expected Incidence Rates

Eight malignancies (excluding non-melanoma skin cancers) were observed in adalimumab-treated patients within the adequate and well controlled studies, and none were observed among placebo-treated patients. Thirty malignancies (excluding non-melanoma skin cancers) were observed in adalimumab-treated patients within the clinical development program, and none were observed among placebo-treated patients (Table 65). Six patients died of their malignancies. Adalimumab-treated patients had approximately an eight-fold greater safety observational exposure in the studies than did placebo-treated patients. Matching the data from the SEER database to the age and sex distribution seen in all patients treated with adalimumab, the expected number of cancers was 22.

In the clinical development program, based on this smaller initial database, a higher SIR rate for malignancies was suggested (Table 65).

**Table 65 : ISS : Malignancies in the Clinical Development Program**

| | Malignancy incidence | | SIR (Standardized Incidence Ratio) [95% CI] | Exposure (patient-years) |
|---|---|---|---|---|
| | Observed incidence | Expected Incidence [1] | | |
| **Adequate and Well-Controlled Studies** | | | | |
| Malignancies in adalimumab-treated | 8 | 6 | | |
| Malignancies in placebo-treated | 0 | 0.8 | | |
| **Clinical Development Program** | | | | |
| Malignancies in adalimumab-treated | 30 | 22 | 1.33 [0.9, 1.9] | 2,954 |
| Malignancies in placebo-treated | 0 | 2.9 | | 385 |

[1] Matching data from NCI SEER database to calculate expected age-matched malignancy rate

for US population (SEER Program Public-Use Data 1973-1998)

These thirty malignancies (excluding non-melanoma skin cancers) were observed among 2334 adalimumab-treated patients over a median of 12 months during the clinical development program and were submitted with the BLA. The most frequently seen malignancies were breast (4), prostate (4), gastrointestinal (4), non-Hodgkin's lymphoma (4), uterine/endometrial (3), and melanoma (2) [Table 66].

Thirty-six non-melanoma skin cancers and 48 malignancies of various types were observed in 2468 RA patients treated in clinical trials with adalimumab for a median of 24 months and were submitted with the final safety update through August 31, 2002. The malignancies observed during use of adalimumab were neoplasms of the immune system (9), breast (7), colon-rectum (6), uterine-cervical (5), prostate (5), melanoma (3), gallbladder-bile ducts (2), and other carcinomas.

**Table 66 : ISS : Cancer Incidence Analysis in Clinical Development Program**

| Cancer Site | Observed in BLA [1] | Observed in Interim Safety Update [2] | Observed in Final Safety Update [3] |
|---|---|---|---|
| **Exposure** | **2334 patients median 12 months** | **2467 patients median 19.3 months** | **2468 patients median 24 months** |
| **All Sites** | **30** | **38** | **48** |
| **All lymphomas** | **4** | **8** | **10** |
| **NHL** | | **7** | |
| **Hodgkin's D** | | **1** | |
| **Breast** | **4** | **5** | 7 |
| **Colon – rectum** | **3** | **4** | **6** |
| **Cervix – Uteri** | **3** | **3** | **5** |
| **Prostate** | **4** | **4** | **5** |
| **Melanoma** | **2** | **2** | **3** |
| **Gallbladder – bile ducts** | **1** | | **2** |
| **Adenocarcinoma (unknown origin)** | **2** | | **2** |
| **Other** | **7** | **11** | **8** |
| **Non-melanoma skin cancers** | **24** | **32** | **36** |
| **Basal cell** | | **23** | |
| **Squamous cell** | | **9** | |

1 Data available through August 31, 2001
2 Data available through March 29, 2002
3 Data available through August 31, 2002

Based on 46 of the 48 malignancies observed in the final safety update, for which data was available to up-date the observed Standardized Incidence Ratio (SIR), the observed SIR (ratio of observed rate to age-adjusted expected frequency) for malignancies was 1.00 (95% CI, 0.7, 1.3)] [Table 67], implying that the observed frequency of malignancies among adalimumab-treated patients was within the expected incidence range.

**Table 67: ISS : Comparative Expected Cancer Incidence Rates In the Adalimumab Clinical Development Program Through August 31, 2002**

| Cancer Type * | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|
| **All Sites** | 46 | 45.82 | 1.00 | (0.7 – 1.3) |
| **All Lymphomas** | 10 | 1.85 | 5.42 | (2.6 – 10.0) |
| **NHL** | 9 | 1.70 | 5.28 | (2.4 –10.0) |
| **Hodgkin's Disease** | 1 | 0.14 | 7.09 | (0.1 – 39.5) |
| **Breast** | 7 | 11.15 | 0.63 | (0.3 – 1.3) |
| **Colon** | 5 | 4.75 | 1.05 | (0.3 – 2.5) |
| **Lung** | 1 | 6.67 | 0.15 | (0.0 – 0.8) |
| **Melanoma** | 3 | 1.53 | 1.97 | (0.4 – 5.7) |
| **Prostate** | 5 | 4.45 | 1.12 | (0.4 – 2.6) |
| **Uterine** | 4 | 2.30 | 1.74 | (0.5 – 4.4) |
| **Other sites** | 11 | 13.12 | 0.84 | (0.4 – 1.5) |
| **Non-Melanoma Skin Cancers** ** | | | | |
| **Basal Cell** | 23 | 20.12 | 1.14 | (0.7 – 1.7) |
| **Squamous Cell** | 9 | 3.79 | 2.37 | (1.1 – 4.5) |

* Cancer rates used were 1992-1999 SEER rates
** Skin cancer rates used were 1977-1978 NCI study rates

A total of ten lymphomas, primarily Non Hodgkin's lymphoma, were observed in patients treated with adalimumab. Based on these patients, the observed SIR (ratio of observed rate to age-adjusted expected frequency) for all lymphomas was 5.4 (95% CI, 2.6, 10.0). The wide confidence interval seen for Non Hodgkin's lymphoma did not allow an accurate determination of whether its frequency was greater than expected. An attempt was made to correlate the onset of the lymphomas and the duration of therapy with adalimumab. Analysis of the exposure interval between initiation of adalimumab treatment and time-to-onset of lymphoma did not provide clear evidence of a relationship between longer duration-of-therapy and incidence of lymphoma (Table 68).

**Table 68 : ISS : Lymphoma Incidence Rates by Duration of Treatment with Adalimumab**

| Exposure Interval Until Time of Event - Months | Number/Total (%) | N(N/100 patient-years) |
|---|---|---|
| 0 - < 6 | 2/2468 (0.08) | 2 (0.2) |
| 6 -< 12 | 1/2216 (0.05) | 1 (0.1) |
| 12 - <18 | 1/1867 (0.05) | 1 (0.1) |
| 18 - < 24 | 2/1395 (0.14) | 2 (0.4) |
| 24 - < 30 | 1/619 (0.16) | 1 (0.4) |
| 30 - < 36 | 0/375 (0.00) | 0 (0.0) |
| 36 - < 42 | 0/321 (0.31) | 1 (0.8) |

Table 69 summarizes the cases of lymphoma observed during the adalimumab clinical development program by type and concomitant therapy. Lymphomas that have occurred in the setting of impaired immune function have most often been large B cell, Non Hodgkin's lymphomas.[5] Similarly, the lymphoma type most often reported in this clinical development program was the large B cell, Non Hodgkin's lymphoma. Ninety percent of the lymphoma patients had received MTX (seven were receiving concomitant MTX and two had received prior MTX), and 80% were receiving concomitant corticosteroids.

**Table 69 : ISS : Summary of Lymphoma Cases By Type and Concomitant Therapy**

| Subject/Study | Type of Lymphoma | Family History | Concomitant Therapy | | |
|---|---|---|---|---|---|
| | | | Azathioprine/ Cyclophosphamide | MTX | CSTD |
| 2204/DE007 | Mantle zone B cell | Sister-leukemia | | X | X |
| 69/DE001 | Diffuse Large B cell | | | X P | |
| 1414/DE011 | MALT cell B cell | | X P | X P | X |
| 8911/DE019 | Follicular B cell | | | X | |
| 10509?DE031 | Large B cell | | | | X |
| 1705/De019 | Mixed small and large B cell | | | X | |
| 11601/DE031 | T cell | | | X | X |
| 8208/DE019 | Small and large B cell | | | X | X |
| 14605/DE031 | Large B cell | | | X | X |
| 4404/DE019 | Hodgkin's | | | X | X |
| Total = 10 | | 1 | 1 | 9 | 8 |

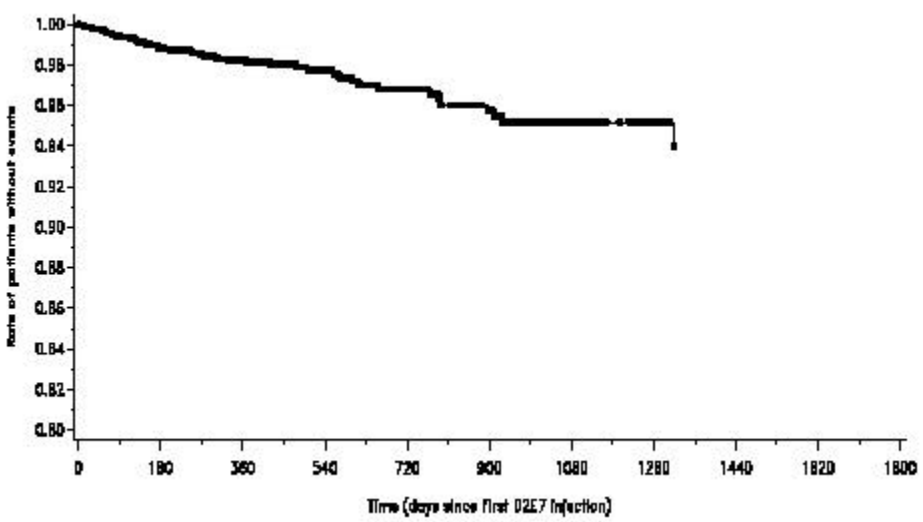
P = previous

[5] Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the FDA. *Arthritis and Rheumatism* 2002;**46**: 3151-3158

Among non- melanoma skin cancers, squamous cell carcinomas also occurred at a frequency greater than expected (Table 67). However, the data used to establish the expected rate were from 1977-1978, leading to some uncertainty of the comparison.

The Kaplan Meier plot in Figure 14 shows that the rate of detection of new malignancies (based on the August 31, 2001 data) was constant over the observation period for all patients treated with adalimumab. The plot does not support an association between increased development of malignancy and longer duration of exposure to adalimumab. If the risk had increased over time, the slope of the curve would become increasingly negative with time. Longer duration of observation will be required to determine whether exposure beyond 2 to 3 years is associated with a higher risk of malignancy.

**Figure 14 : ISS : Kaplan Meier curve of time to first malignancy during treatment with adalimumab in all patients treated with adalimumab**




In this clinical development program malignancies were observed at frequency rates approximating the expected rate, except for neoplasms of the immune system which were observed at a greater rate than expected. Since the introduction of TNF blocking agents which affect host defenses by modulating cellular immune responses, a major concern of the Agency has been the possibility of an increased risk of development of lymphomas among patients treated with TNF blocking agents. Published literature suggests that RA patients with highly active disease have a greater risk of lymphomas. Two published epidemiologic studies of 11,683 [6] and 1,767 [7] patients observed an approximately 4 to 5 fold increased incidence of lymphoma in patients with moderately active RA. The RA patients who participated in this clinical development program all had moderate to severe RA with mean duration of disease above 10 years.

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[6] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis : nested case-control study. *BMJ* 1998; **517**: 180-1

[7] Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts Non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients. *ACR Plenary II* 1998: **931**

Available data are insufficient to determine whether adalimumab increases the incidence of lymphomas above that expected in this patient population. Continued monitoring of adalimumab-treated patients is necessary to quantify the role of adalimumab, if any, in contributing to the high observed incidence of lymphomas.

### G. Serious Infections

Since the introduction of TNF blocking agents like adalimumab that modulate cellular immunity, development of serious infections among patients treated with anti-TNF agents has been a major concern of the Agency. In the adalimumab clinical development program, serious infections were defined as infections associated with hospitalization or with use of parenteral antibiotics. Forty-one patients (34 [3%] of 1380 adalimumab-treated patients [4.3 patients/100 pt-yrs] and 7 [1%] of 690 placebo-treated patients [1.9 patients/100 pt-yrs]) experienced serious infections, as provided in the BLA data available through Aug 31, 2001. Four adalimumab-treated patients experienced two serious infections each; the remaining 37 patients experienced a single serious infection. Two patients died of infectious AEs, and 13 patients withdrew from the studies as a result of serious infections. The most common organs involved in the infections were the respiratory, skin, musculoskeletal, gastrointestinal, and genitourinary (Table 70).

**Table 70 : ISS : Organ involvement for serious infections excluding tuberculosis and Opportunistic infections – (Data Available through August 31, 2001)**

| Body system | Type of Infection | Number |
|---|---|---|
| Respiratory | Pneumonia | 29 |
| | Bronchitis | 6 |
| | Laryngitis | 2 |
| | Flu-Syndrome | 2 |
| | Sinusitis | 1 |
| | Cough Increased | 1 |
| Skin | Cellulitis | 10 |
| | Wound Infection | 7 |
| | Herpes Zoster | 6 |
| | Abscess | 6 |
| | Digit Infection | 3 |
| | Necrotizing Fasciitis | 1 |
| Genitourinary | Urinary Tract Infection | 10 |
| | Pyelonephritis | 4 |
| | Cystitis | 3 |
| Musculoskeletal | Septic Arthritis | 9 |
| | Infected Prosthesis | 2 |
| | Osteomyelitis | 2 |
| | Bursitis | 1 |
| | Spondylodiscitis | 1 |
| Gastrointestinal | Diverticulitis | 7 |
| | Appendicitis | 4 |
| | Viral Gastroenteritis | 2 |
| | Infectious Diarrhea | 1 |
| Other | Sepsis | 4 |
| | Otitis Media | 1 |
| | Bacteremia | 1 |
| | Bacterial Infection | 1 |
| | Endocarditis | 1 |

Table 71 presents the different kinds of serious infections observed during the adequate and well-controlled studies.

**Table 71 : ISS : Patients with serious infections – adequate and well-controlled studies**

| Study | Pt. No. | Age, sex | Treatment | Adverse event (HARTS term) | Adverse event (Investigator's term) | Day on drug at onset | Duration (days) |
|---|---|---|---|---|---|---|---|
| DE009 | 2301 | 68, M | Adalimumab 40 mg eow | Pneumonia | Pneumonia | 150 | 18 |
| | 3006 | 76, F | Adalimumab 40 mg eow | Gastrointestinal disorder | Diverticulitis | 113 | 8 |
| | 3421 | 63, M | Adalimumab 80 mg eow | Pneumonia | Pneumonia | 147 | 17 |
| DE011 | 114 | 45, F | Adalimumab 40 mg wk | Arthritis[a] | Septic arthritis | 95 | 11 |
| | 305 | 73, M | Adalimumab 40 mg eow | Pneumonia | Pneumonia | 103 | 23 |
| | 524 | 76, F | Adalimumab 20 mg wk | Pneumonia | Pneumonia | 46 | 25 |
| | 1402 | 35, F | Adalimumab 20 mg wk | Flu syndrome | Flu-like syndrome | 130 | 2 |
| | 1420 | 33, F | Adalimumab 40 mg wk | Cystitis | Cystitis | 128 | 4 |
| | 1910 | 46, M | Adalimumab 20 mg wk | Pyogenic arthritis[a] | Septic arthritis | 54 | 41 |
| | 2820 | 58, F | Adalimumab 40 mg wk | Sinusitis | Right maxillary sinusitis | 79 | 124 |
| | 3501 | 61, F | Adalimumab 20 mg eow | Sepsis | Urosepsis | 162 | 29 |
| | | | | Cough increased | Cough | 180 | 38 |
| | 4009 | 64, F | Adalimumab 20 mg wk | Urinary tract infection | Urinary tract infection | 30 | unk |
| | 4411 | 61, F | Adalimumab 20 mg eow | Sepsis[a] | Sepsis | 90 | 11 |
| | 4913 | 73, F | Adalimumab 20 mg wk | Infection | Erysipelas | 18 | 13 |
| DE019 | 1110 | 41, F | Placebo | Pneumonia | Pneumonia | 192 | 10 |
| | 2205 | 71, F | Adalimumab 40 mg eow | Gastrointestinal disorder[a] | Diverticulitis | 73 | 20 |
| | | | | Pneumonia[a] | Pneumonia | 73 | 20 |
| | 2405 | 63, M | Adalimumab 40 mg eow | Urinary tract infection | Urinary tract infection | 112 | 4 |
| | 2419 | 50, F | Adalimumab 40 mg eow | Pneumonia[a] | Pneumonia | 214 | NA |
| | 2704 | 67, F | Adalimumab 20 mg wk | Gastroenteritis | Viral gastroenteritis | 26 | 3 |
| | 2902 | 73, F | Adalimumab 40 mg eow | Pneumonia[a] | Bilateral pneumonitis | 48 | 8 |
| | 3205 | 56, F | Adalimumab 20 mg wk | Pyelonephritis | Pyelonephritis | 131 | 31 |
| | 3416 | 66, M | Adalimumab 40 mg eow | Herpes zoster[a] | Disseminated herpes zoster | 85 | 68 |
| | 3813 | 28, F | Adalimumab 40 mg eow | Tuberculosis reactivated[a] | Tuberculosis | 106 | NA |
| | 3901 | 70, M | Adalimumab 40 mg eow | Pneumonia | Pneumonia | 58 | 3 |
| | 5503 | 59, M | Adalimumab 40 mg eow | Pneumonia | Pneumonia | 348 | 73 |
| | 5706 | 79, M | Adalimumab 20 mg wk | Urinary tract infection | E. coli urosepsis | 149 | 5 |
| | 6210 | 71, F | Adalimumab 40 mg eow | Infection[a] | Histoplasmosis | 77 | NA |
| | 7811 | 73, F | Adalimumab 40 mg eow | Bronchitis | Bronchitis | 308 | 22 |
| | 8702 | 75, F | Adalimumab 40 mg eow | Urinary tract infection | E. coli urosepsis | 115 | 14 |
| | | | | Sepsis | Septic shock | 115 | 14 |
| | 8910 | 70, F | Adalimumab 20 mg wk | Pneumonia | Pneumonia | 262 | 5 |
| | 9908 | 53, M | Adalimumab 20 mg wk | Infection[a] | Foot infection | 113 | 5 |
| DE031 | 10708 | 78, F | Placebo | Bronchitis | Acute bronchitis | 5 | 5 |
| | 10711 | 66, F | Placebo | Colitis | Colitis | 116 | 4 |
| | 10712 | 72, F | Placebo | Bronchitis | Acute bronchitis | 163 | 4 |
| | 11613 | 61, M | Adalimumab 40 mg eow | Infection[a] | Foot infection | 81 | 45 |
| | 11614 | 62, M | Placebo | Pneumonia[a] | Pneumonia | 92 | 5 |
| | 12001 | 43, F | Adalimumab 40 mg eow | Gastrointestinal disorder | Appendicitis | 34 | 5 |
| | 12603 | 23, M | Adalimumab 40 mg eow | Gastrointestinal disorder | Appendicitis | 3 | 2 |
| | 15006 | 58, F | Placebo | Abscess[a] | Epidural abscess | 72 | NA |
| | 15106 | 70, M | Adalimumab 40 mg eow | Herpes zoster | Disseminated herpes | 11 | 16 |
| | | | | Tendon disorder | Necrotizing fasciitis | 11 | 16 |
| | 15714 | 44, F | Placebo | Pneumonia | Pneumonia | 84 | 10 |

F = female M = male wk = weekly eow: every other week

unk: = unknown NA = not applicable

[a] Resulted in permanent withdrawal.

Infections that were associated with sepsis during the clinical development program are listed in Table 72. Skin, musculoskeletal and urinary infections were among those infections most frequently associated with sepsis.

**Table 72 : ISS : Infections Associated with Sepsis During the Adalimumab Clinical Development Program**

| Body system | Type of Infection | Number |
|---|---|---|
| Genitourinary | Urinary Tract Infection | 3 |
| Musculoskeletal | Spondylodiscitis | 1 |
| | Infected Prothesis | 1 |
| Skin | Cellulitis | 1 |
| | Abscess | 1 |
| | Necrotizing fasciitis | 1 |
| Other | Bacteremia | 1 |
| | Sepsis | 3 |

Table 73 summarizes all patients who experienced serious infections, including the 4-month interim and final safety up-dates.

**Table 73 : ISS : Overview of Serious Infections of Clinical Interest As Reported in the ISS, Interim 4-Month Safety Update, and Final Safety Update**

| Patients with Any | Safety Data and Up-Dates | | | Total |
|---|---|---|---|---|
| | ISS BLA Submission [1] | 4-Month Interim Up-Date [2] | Final Up-Date [3] | |
| SAE | **575** | **241** | **160** | **976** |
| Serious infection | **129** | **35** | **38** | **202** |
| Tuberculosis | 9 | 1 | 3 | **13** |
| Opportunistic Infection | 2 | 1 | 3 | **6** |

[1] The ISS reported safety data through 31-Aug-2001 included in the original submission
[2] The 4-month safety update data from 31-Aug-2001 through 29-March-2002 and data that had not been reported in the original submission
[3] This safety update reported data from 29-March-2002 through 31-Aug-2002

A total of 202 adalimumab-treated patients (includes the final safety up-date of 31-Aug-2002) experienced serious infections during the clinical development program. Review of information provided on 186 subjects with serious infections, revealed a wide assortment of serious infections. Based on this larger safety database, the order of frequency remains similar; the serious infections observed were pulmonary, musculoskeletal (including post-surgical), skin, gastrointestinal, and genitourinary.